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In the Claims

1. (Amended) [A] An aspartic acid protease inhibitor comprising two or more transition-state isosteres.

4. (Amended) The composition of claim 1 [inhibitor of claim 3] 1 wherein the aspartic acid protease inhibitor [inhibits] is an HIV protease inhibitor.

7. (Amended) A method for treating a patient infected with a pathogen expressing [a] an aspartic acid protease comprising the oral administration of [administering a] an aspartic acid protease inhibitor comprising two or more transition-state isosteres.

10. (Amended) The method of claim [9] 7 wherein the protease inhibitor inhibits HIV protease.

Please cancel claims 3 and 9.

Drawings

Attached to the Office Action, mailed on March 8, 2001, was a Notice of Draftperson's Patent Drawing Review which indicated that several of the drawings filed February 18, 2000 are objected to under 37 C.F.R. 1.84 and 1.48. However, please note that Applicants submitted

formal drawings, on September 14, 2000, to the Official Draftsperson of the Drawing Review Branch. Enclosed with this Response are copies of the previously submitted formal drawings.

Amendments to the Claims

The present invention is directed to aspartic acid protease inhibitors containing two or more transition state isosteres and a method of using such protease inhibitors to treat patients.

Claims 1-12 are pending. Claims 1, 4, 7, and 10 have been amended. Claims 3 and 9 have been canceled. Claims 1 and 7 have been amended to define the protease as an aspartic acid protease. Support for the amendments to claims 1 and 7 can be found, for example, on page 5, lines 24-26. The method of claim 7 has been further amended to incorporate the oral administration of an aspartic acid protease inhibitor. Support for the oral administration of an inhibitor can be found, for example, on page 12, lines 29-30. Claim 4 has been amended to be dependent from the composition of claim 1 and more clearly define the inhibitor as an HIV protease inhibitor. Support for the amendment made to claim 4, can be found, at least, within the Examples provided and on page 5, lines 23-26. Claim 10 has been amended to depend from claim 7. Support for the amendment to claim 10, can be found for example, on page 12, lines 27-33. A copy of all of the pending claims as they are believed to have been amended is attached to this Amendment as an appendix.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-12 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The examiner asserts that the critical core structure necessary for biological activity is not defined by the applicant. However, the aspartic acid proteases comprise a family of proteases that utilize a similar catalytic mechanism involving aspartic acid residues (see Figure 5 in Marciniszyn et al., J. Biol. Chem. 251(22):7088-7094 (1976), reference submitted with Information Disclosure Statement mailed on July 25, 2000), which is extremely well known. The similarity in mechanism leads to a similarity in transition state structure, which, in turn, leads to inhibition by a similar class of inhibitors. Thus, all of the protease inhibitors designed to inhibit a single aspartic acid protease are expected to inhibit all aspartic acid proteases. This class of inhibitors clearly delineates the core structure that would be necessary for biological activity. The common core structure, as defined by the transition state structure, enables these inhibitors to be grouped into one class.

The independent claims have been limited to an aspartic acid protease inhibitor comprising two or more transition state isosteres as a composition and using this composition in a method to treat an infected patient by oral administration. Those of skill in the art know how to make and use isostere structures. Those of skill also know the purpose of transition state isosteres. As stated in the paragraph bridging pages 3 and 4 of the specification, many types of isosteres are well known and their mechanism of action is predictable based upon, for example, the fact that "a single transition-state isostere is used in an inhibitor since it mimics a substrate peptide with a single hydrolysis site". The drugs that have proven to be clinically effective, especially in the case of HIVPr inhibition, and are commercially available, provide further evidence of just how well known this type of mechanistic action of inhibition is. Therefore, one

skilled in the art would be very familiar with isostere structures and the processes used to synthesize them. Based on their mechanism of protein inhibition and precedent set with isostere containing compounds such as renin, methods incorporating isostere compounds to treat patients are well known. Therefore, it would not require undue experimentation for one of ordinary skill in the art to make or use inhibitors containing two or more isosteres from the disclosure coupled with information known in the art regarding isostere containing compounds.

The *de novo* design of protease inhibiting compounds requires one to characterize the target protease as a member of either the serine, cysteine, metallo, or aspartyl class. Once the protease to be inhibited has been designated, the protocol to design the inhibitor can be determined without undue experimentation because as stated on lines 29-3, bridging pages 3 and 4 of the specification, the aspartic proteases share a common active-site structure and catalytic mechanism. The design of other inhibitors, for such aspartic proteases as renin and HIVPr, has been demonstrated based on this principal.

The claimed aspartic protease inhibitor is adequately described within the specification. The process of making an inhibitor containing two isosteres and its efficacy against resistance is demonstrated in the Examples. UIC-98-056 contains two isosteres and is an aspartic protease inhibitor as proven by its inhibition of HIVPr. The class of aspartic protease inhibitors, by definition, are not divergent in size and properties because of their predictability and stereospecificity for a class of proteases with similar active pockets to which they bind and interact.

The examiner asserts that the claims broadly encompass the incorporation of an unlimited number of types of compounds into a pharmaceutical composition and, more specifically, the formation of pharmaceutical compositions containing different therapeutic agents that vary in size, physical and chemical properties, for *in vivo* delivery. This is simply not accurate. The claims require the inhibitor be an aspartic acid protease inhibitor containing two or more isosteres. Therefore, the claims define the class of inhibitors in size, physical and chemical properties as stated above.

The examiner also asserts that the applicants are required to show efficacy and, in not doing so, practice of the invention would require undue experimentation for the skilled artisan. Standard procedures and tests are commonplace within the art in order to identify the type of dosage and therapeutic regimen. Many patients will, undoubtedly, change therapy due to treatment failure, intolerance and/or non-adherence to a dose schedule. These factors are unavoidable and therefore require unavoidable, yet routine and not uncommon, tests for new considerations of treatment. Tests to elucidate factors such as disease stage are also part of the routine to acquire an effective regimen and dose of protease inhibitor to be administered.

A patent is not required to teach, and it is desired to omit from the specification, what is well known in the art. Engaging in the required experimentation to elucidate the efficacy of a protease inhibitor, given the myriad of obstacles provided above, is typical in the art, not undue.

Another common, routine practice within the art is the determination of the viral load per ml of plasma in a particular patient. The viral load will aid in the determination of the dosage parameters from which to work from. The dosage administered to the patient is, therefore, under

the discretion of the physician. The dosage *parameters* for protease inhibitors, for example HIVPr inhibitors, were clearly established by physicians and well known at the time of filing of the present application. Studies even went so far as to determine the dosage dependent pharmacokinetic interactions of protease inhibitors, such as ritonavir, indinavir, nelfinavir, and saquinavir, with other known protease and reverse transcriptase inhibitors (See Table 1, Carpenter *et al.*, JAMA 280 (1): 78-86 (1998), reference submitted with Information Disclosure Statement mailed on July 25, 2000). These and other protease inhibitors have been shown to be effective and have been approved for treatment. It is well established that these types of protease inhibitors are successful.

Simply put, if the art recognizes that standard modes of administration are known and contemplated, then 35 U.S.C § 112 is satisfied. *In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); *In re Hitchings*, 342 F.2d 80, 87, 144 USPQ 637, 643 (CCPA 1965). If one of ordinary skill in the art, based on the knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, the standard established by 35 U.S.C § 112 is satisfied. Therefore, it would not require undue experimentation for a person skilled in the art to determine the effective protease inhibitor dosage required to effectively treat a patient.

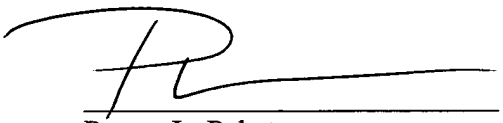
Strategies employed for the treatment of HIV-infected individuals are meant to be long-term because there is not a current cure for the disease. Therefore, a determination must be made on a patient by patient basis because the therapeutic benefit of a strategy over time involves

"balancing potency, tolerance, regimen complexity, adverse effects, risk of resistance and cost".

(Carpenter *et al.*, JAMA 280 (1): 78-86 (1998)).

Allowance of claims 1, 2, 4-8, and 10-12 is respectfully solicited.

Respectfully submitted,



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Date: June 8, 2001

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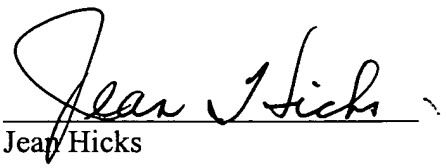
I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.



Jean Hicks

Date: June 8, 2001

Marked Up Version of Amended Claims
Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

1. (Amended) [A] An aspartic acid protease inhibitor comprising two or more transition-state isosteres.

2. The inhibitor of claim 1 wherein the transition-state isostere is -CH(OH)-CH_2-.

Please cancel claim 3.

4. (Amended) The composition of claim 1 [inhibitor of claim 3] wherein the aspartic acid protease inhibitor [inhibits] is an HIV protease inhibitor.

5. The inhibitor of claim 1 which is UIC-98-056.

6. The inhibitor of claim 2 wherein the CH(OH)-CH_2 is substituted with two other kinds of isosteres.

7. (Amended) A method for treating a patient infected with a pathogen expressing [a] an aspartic acid protease comprising the oral administration of [administering a] an aspartic acid protease inhibitor comprising two or more transition-state isosteres.

Please cancel claim 9.

8. The method of claim 7 wherein the transition-state isostere is CH(OH)-CH_2-.

10. (Amended) The method of claim [9] 7 wherein the protease inhibitor inhibits HIV protease.

11. The method of claim 10 wherein the inhibitor is UIC-98-056.

12. The method of claim 8 wherein the CH(OH)-CH_2 is substituted with two other kinds of isosteres.

APPENDIX: CLEAN COPY OF CLAIMS

1. (Amended) An aspartic acid protease inhibitor comprising two or more transition-state isosteres.

2. The inhibitor of claim 1 wherein the transition-state isostere is -CH(OH)-CH_2-.

4. (Amended) The composition of claim 1 wherein the aspartic acid protease inhibitor is an HIV protease inhibitor.

5. The inhibitor of claim 1 which is UIC-98-056.

6. The inhibitor of claim 2 wherein the CH(OH)-CH_2 is substituted with two other kinds of isosteres.

7. (Amended) A method for treating a patient infected with a pathogen expressing an aspartic acid protease comprising the oral administration of an aspartic acid protease inhibitor comprising two or more transition-state isosteres.

8. The method of claim 7 wherein the transition-state isostere is CH(OH)-CH_2-.

10. (Amended) The method of claim 7 wherein the protease inhibitor inhibits HIV protease.

11. The method of claim 10 wherein the inhibitor is UIC-98-056.

12. The method of claim 8 wherein the CH(OH)-CH_2 is substituted with two other kinds of isosteres.

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